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Schizophrenia susceptibility genes converge on interlinked pathways related to glutamatergic transmission and long-term potentiation, oxidative stress and oligodendrocyte viability

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Abstract

Over 130 genes have been associated with schizophrenia in genetic studies. None of these has reached a sufficient level of confidence to be accepted as a universal susceptibility gene and problems of replicability suggest that many may be false positives. Nevertheless, these genes can be grouped into distinct families related to glutamate transmission (in particular related to NMDA receptor function), the control of synaptic plasticity, dopaminergic transmission, oxidative stress, glutathione and quinone metabolism and oligodendrocyte viability. These families mirror the processes disrupted in the schizophrenic brain and certain gene families can be linked together to form a clearly defined signalling cascade involved in the phenomenon of NMDA receptor-dependent long-term potentiation and synaptic plasticity, that may be interconnected with oligodendrocyte and oxidative stress-related pathways. Many of the protein products of these genes interact with each other, forming complex integrated networks. Certain high-interest genes (for example **DISC1**, **NRG1**, **COMT**) may exert multiple effects on different areas of these pathways, while others exert more specific effects on certain branches. The convergence of a large number of genes on a definable signaling network raises the possibility of numerous interactions between gene candidates, and suggests that a targeted multigenic pathway approach would be useful in gene association studies.

Keywords: Polymorphism; Association; Gene; Multigenic; Schizophrenia; NMDA; Dopamine; Glutathione; Quinone; Oxidative stress; Oligodendrocyte

1. Introduction

Schizophrenia is influenced both by genes and the environment. Prenatal exposure to famine or beri-beri (Davis and Bracha, 1996), tick infestation and Lyme disease (Brown, 1994) influenza or rubella (Brown, 2006) have all been associated with an increased risk of developing schizophrenia in later life. These observations, together with reports of increased ventricular volume and decreased cortical volume in later life in schizophrenia (with no evidence of an ongoing neuronal lesion process) (Johnstone et al., 1976; Wright et al., 2000) have contributed largely to neurodevelopmental hypotheses of schizophrenia (Rapoport et al., 2005).

Current hypotheses suggest that schizophrenia is characterised by hypoglutamatergic and hyperdopaminergic function. It is believed that the disease is related to over stimulation of subcortical **DRD2** dopamine receptors, hypoactivity of frontal cortical DRD1 dopamine

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receptors and reduced prefrontal glutamatergic activity (Goldman-Rakic et al., 2004; Laruelle et al., 2003). There is also evidence for synaptic changes in many brain regions, reflecting a reorganisation of synaptic inputs and reductions in dendritic length, spine density and arborisation of receptive cells. These changes have been observed in the prefrontal and temporal cortex, hippocampus and caudate nucleus (Black et al., 2004; Garey et al., 1998; Glantz and Lewis, 2000; Kung et al., 1998; Rosoklija et al., 2000; Selemon and Goldman-Rakic, 1999) and constitute a major feature of schizophrenic pathology. Decreases in glutamate decarboxylase expression (GAD67/**GAD1**) in subsets of parvalbumin containing GABAergic neurones have also been observed in the frontal cortex (Lewis et al., 2004). Schizophrenia is also characterised by astrocytic malfunction and oligodendrocyte cell loss. A summary of multiple studies of prefrontal cortical tissue from schizophrenic brains from the Stanley consortium highlighted a consensus for a decrease in GFAP levels and oligodendrocyte number, a feature also observed in major depression and bipolar disorder (Knable et al., 2001; Uranova et al., 2001, 2004). Apoptosis and necrosis of oligodendrocytes has been reported in the frontal cortex and caudate nucleus in both schizophrenia and bipolar disorder (Uranova et al., 2001).

Decreases in oligodendrocyte density of ~20–30% have been observed in various frontal cortical regions in schizophrenia (Hof et al., 2002, 2003; Uranova et al., 2004) (Vostrikov et al., 2004). The immunoreactivity of the oligodendrocyte-associated markers 2′,3′-cyclic nucleotide 3′-phosphodiesterase (**CNP**) and myelin-associated glycoprotein (**MAG**)is reduced by a similar magnitude (Flynn et al., 2003). Microarray studies have also demonstrated a generalised reduction in the expression of oligodendrocyte and myelinisation associated gene messages in the schizophrenic brain (Hakak et al., 2001; Katsel et al., 2005a).

Schizophrenia is also characterised by a large reduction in cerebral and CSF glutathione levels in life (Do et al., 2000). Levels of 5-*S*-cysteinyl DOPAC and 5-*S*-cysteinyl dopamine, the end products of dopamine-derived quinone metabolism are increased in the schizophrenic brain (Carlsson et al., 1994) and a number of publications suggest that free radicals and oxidative stress are implicated in schizophrenia pathology (Mahadik and Scheffer, 1996; Reddy and Yao, 1996; Yao et al., 2001). Recently, a microarray and proteomics study showed that many of the genes and proteins whose expression is modified in the schizophrenic brain are related to glutathione and oxidative stress pathways (Prabakaran et al., 2004).

In parallel with the research that has led to these hypotheses and observations, genetic studies have identified over 130 putative (and highly contested) susceptibility genes that may predispose to schizophrenia in some populations. These genes are the combined result of directed research related to the major schizophrenia hypotheses and of gene selection following genome-wide scans of chromosomes with closely spaced polymorphic markers. This review outlines the function of some of these genes and suggests that they may be organised into a signaling network whose dysfunction may play a key role in schizophrenia.

2. Methods

Genes associated with schizophrenia, or individual gene deletions, repeats or translocations were collected by literature survey and from the Genetic association database (GAD) (Becker et al., 2004) (http://geneticassociationdb.nih.gov) or the Database for Schizophrenia candidate genes focusing on Variations (VSD) (Zhou et al., 2004) (http://bioinfo.tsinghua.edu.cn:8080/vsd/index.php). Linkage data for the chromosomal regions in which these genes are situated were recovered from the Online Mendelian Inheritance in Man database http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=omim) and literature surveys. The selection aimed to include all genes for which at least one association study (either family or case-control studies) concluded that positive association was detected and is based on the interpretation of the original authors. Negative studies have not been included, but these exist for many of the listed genes (see Discussion). This include-all policy allows the presentation of a pool of genes whose implication may be supported/contested by other data. The reasons for this are related to an assumption of genetic heterogeneity in different populations and to possible gene/gene and gene/environment interactions, which may have influenced both negative and positive association studies. The collection assumes that both negative and positive association studies in different populations may be correct (assuming an adequate methodological statistical study) and that there may be an underlying reason for this heterogeneity. These problems are addressed more fully in the discussion. References for positive and negative association studies, together with details of each polymorphism and links to other databases can also be found in both the GAD and VSD databases for most genes. I have not detailed the individual polymorphisms. The review is concerned with identifying the common properties of sets of genes implicated in schizophrenia, and their global

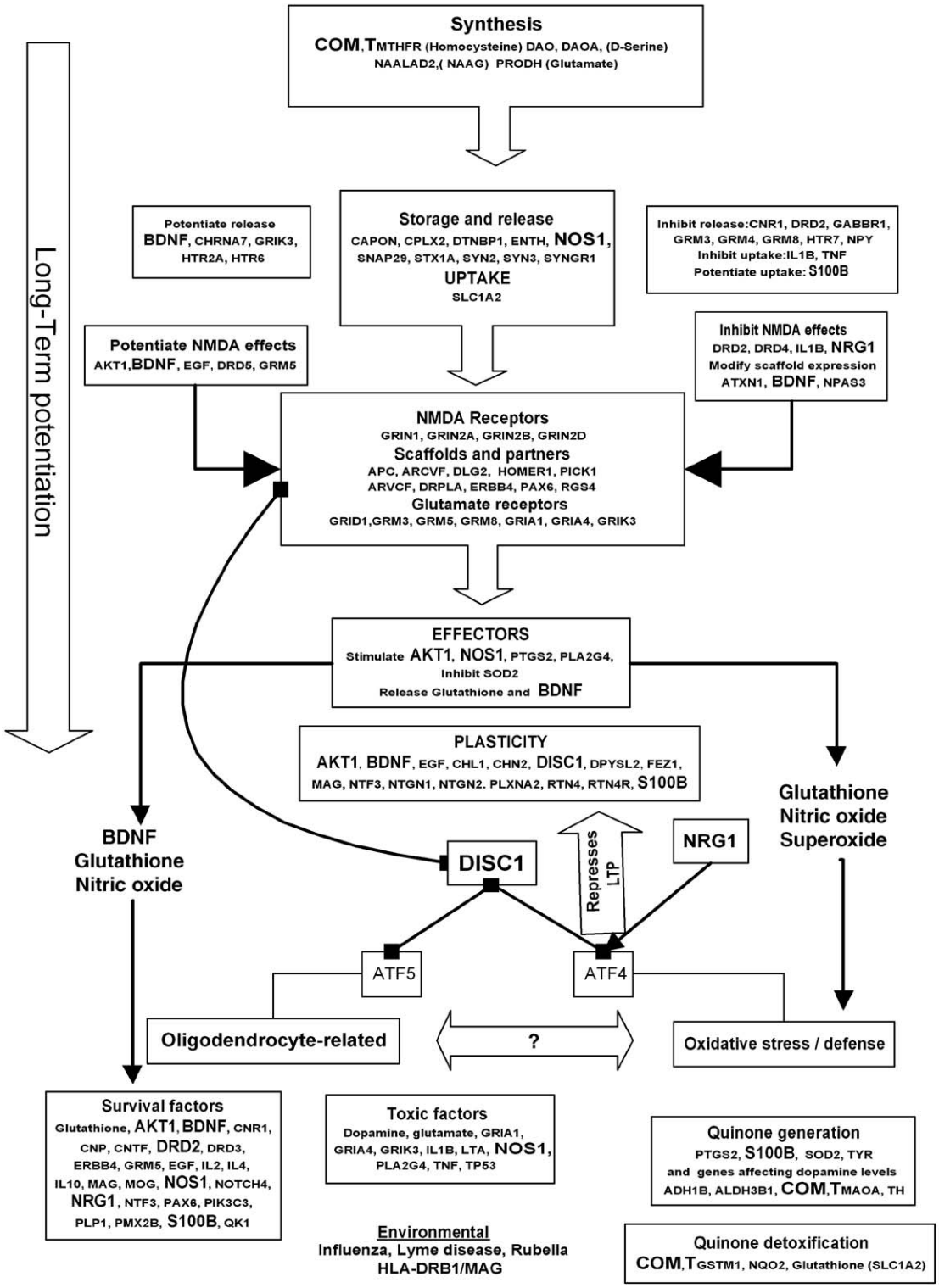


Fig. 1. Genes associated with schizophrenia can be grouped into families and organised into a signalling cascade involved in the generation of NMDA-receptor dependent long-term potentiation and the control of synaptic plasticity. Other genes families are related to oxidative stress and to oligodendrocyte viability. The potential role of **DISC1** as a transduction hub between these pathways is illustrated. This suggestion is based solely on an analysis of the role of the binding partners of **DISC1** revealed in yeast two-hybrid studies and remains to be experimentally verified. Genes in larger typeface illustrate an involvement in several of the processes illustrated. See text and website (Carter, 2006) for references.

interrelations in a signaling network, rather than with their individual variation.

Because of the large number of citations generated by so many genes, chromosomal location, association and linkage references and other effects are not always referenced in the main text but are available in the supplementary .html table, where case and family association studies are listed by country of origin. These data are posted at http://www.polygenicpathways.co.uk/ with hyperlinks to ENTREZ Gene, OMIM data and PUBMED. A brief summary of function, binding partners and expression data in schizophrenia is also provided. Where available, the relationships of particular polymorphisms to protein function are provided. Genes associated with schizophrenia in at least one study are grouped into functional classes based mainly on ENTREZ gene data (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene) which are referenced by the Gene ID rather than by the original source. Other reasons for ascribing genes to a particular family are referenced when necessary. Binding interactions between proteins are also culled from the ENTREZ database, except where specifically cited. Throughout the text, gene symbols for genes associated with schizophrenia are shown in **bold**. Gene symbols are those approved by the HUGO gene nomenclature committee (Wain et al., 2002). (http://www.gene.ucl.ac.uk/nomenclature/).

3. Results

Genes associated with schizophrenia can be grouped into families that control similar processes. For example, **DAO, DAOA, MTHFR, NAALAD2, PRODH** and **SLC1A2** (Table 1) would all affect the availability of glutamate, and in particular NMDA, receptor agonists.

CPLX2, **SNAP29**, **SYN2**, **SYN3**, **SYNGR1** and **STX1A** are all components, and **CAPON**, **DTNBP1** and **ENTH**, associates or regulators of the SNARE complex that regulates glutamate storage and release (Calakos and Scheller, 1996) **CNR1**, **DRD2**, **GRM3**, **GRM4**, **GRM8**, **GABBR1** and **HTR7** receptor agonists all inhibit glutamate release, which is stimulated by **CHRNA7**, **GRIK3**, **HTR2A**, **HTR6** and **HTR7** receptor agonists. **IL1B** and **TNFA** inhibit glutamate uptake, which is potentiated by **S100B** (Table 2).

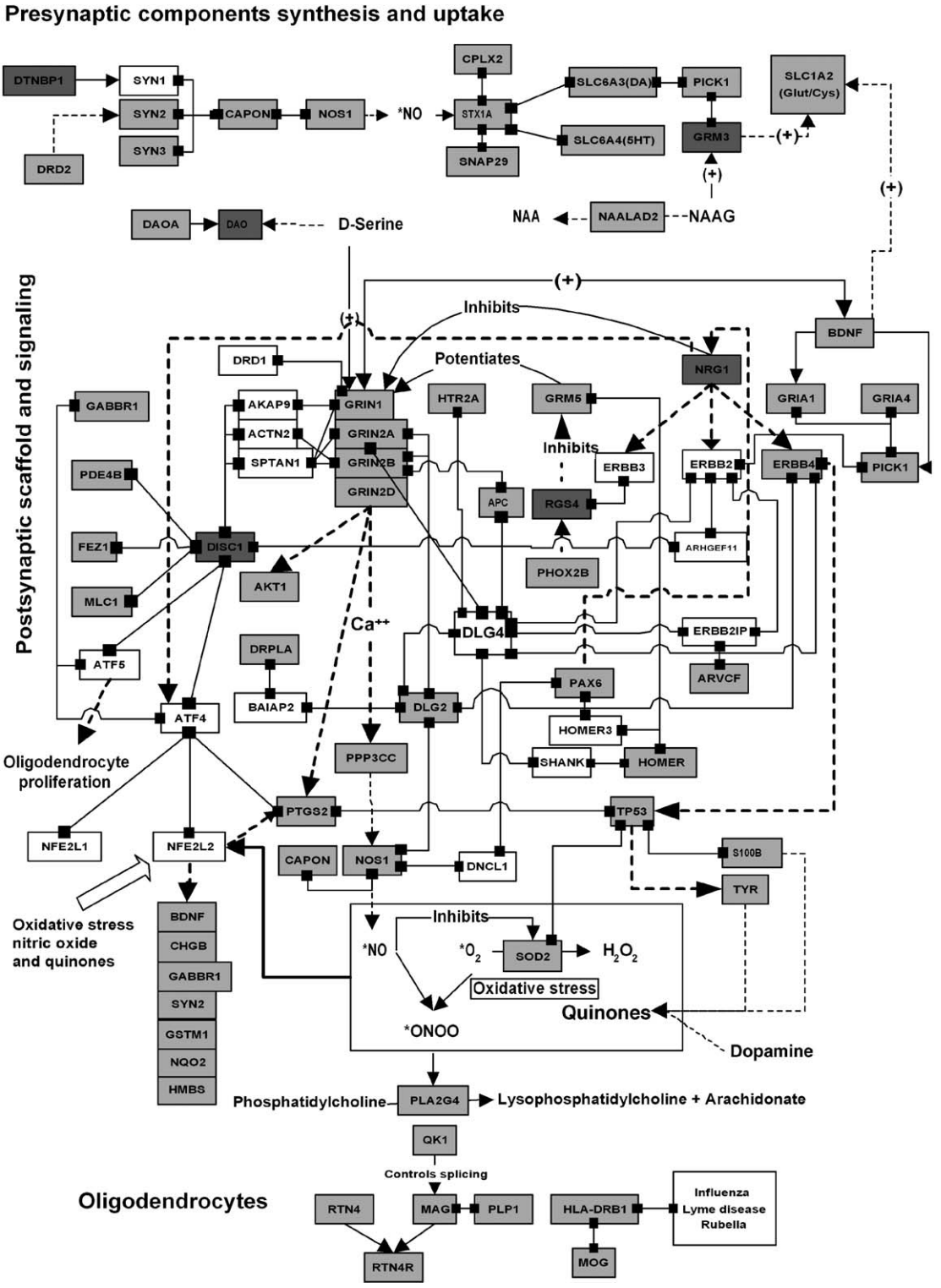
DLG2, **HOMER1** and **PICK1** are all components of the postsynaptic scaffold that regulates glutamate and neuregulin (**NRG1**) receptor clustering. **ARVCF**, **APC ATXN1**, **DRPLA**, **NPAS3**, **PAX6**, **RGS4** and **ZDHHC8** colocalise with, bind to, or control the expression of postsynaptic glutamate or **NRG1** receptors (**ERBB4**) and scaffold proteins (Table 3).

GRIN1, **GRIN2A**, **GRIN2B** and **GRIN2D** (Table 3) code for subunits of the NMDA receptor that couples to nitric oxide synthase (**NOS1**) (Brenman and Bredt, 1997), whose activity is regulated by calcineurin (**PPP3CC**) (Rameau et al., 2003) and which binds to **CAPON** (Jaffrey et al., 1998). **NRG1** controls the internalisation of the NMDA receptor subunit **GRIN1** (Gu et al., 2005). NMDA receptor activation also stimulates cyclo-oxygenase-2 (**PTGS2**) and cytosolic phospholipase A2 (**PLA2G4**) activity and inhibits that of superoxide dismutase (**SOD2**). **HMBS** provides the heme cofactor necessary for **NOS1** and **PTGS2** activity (See Table 4).

DISC1 binding partners identified by two-hybrid studies (Millar et al., 2003; Morris et al., 2003) include a number of proteins that themselves interact with glutamate receptors. These include AKAP9, which binds to **GRIN1** (Feliciello et al., 1999) alpha-actinin (ACTN2) which binds to both **GRIN1** and **GRIN2B** (Wyszynski et al., 1997) and alpha-fodrin/spectrin (SPTAN1) which binds to **GRIN1**, **GRIN2A** and **GRIN2B** (Wechsler and Teichberg, 1998). The **DISC1** binding partner ARHGEF11 also forms a complex with the **NRG1** receptor ERBB2 and plexin B1 (Swiercz et al., 2004). The carboxy terminus of wild-type **DISC1** (but not the form truncated in certain schizophrenia cases) interacts with transcription factors ATF4 and ATF5 (Morris et al., 2003), as does the GABAb receptor **GABBR1** (White et al., 2000). ATF4, which is also activated by **NRG1** (Talukder et al., 2000), controls the resistance of cells to oxidative and other stressors and regulates the transcription of glutathione synthesis related genes (Harding et al., 2003; Rutkowski and

Fig. 2. An interaction map illustrating some of the protein/protein interactions between the various products of selected schizophrenia-related genes. Control of gene expression by transcription factors (**PAX6**, **PHOX2B**, NFE2L2) is also shown. These interactions were collected from the literature or from information in the interactions section of the ENTREZ gene entries (See text and/or website (Carter, 2006) for references). Genes reportedly associated with schizophrenia are highlighted by grey boxes. Dark grey boxes represent current high-interest genes. The scheme is not intended as a physiological representation of a glutamatergic synapse but simply reports the binding and other interactions between pairs of individual proteins. Ternary or other multicomplexes should not be inferred. Solid lines and squares represent binding interactions between partners, Dashed lines and arrows represent effects on activity, expression or metabolic reactions. NAA = *N*-acetylaspartate; NAAG = *N*-acetyl aspartylglutamate. DLG4 (psd-95) binds to all NMDA receptor subunits represented.

Kaufman, 2003). ATF4 also acts to repress LTP and a genetically engineered inhibition of ATF4 in mice enhances LTP, memory formation and synaptic plasticity in mice (Chen et al., 2003). ATF5 controls the proliferation and differentiation of oligodendrocytes (Mason et al., 2005).



NMDA receptor activation results in long-term potentiation (LTP), a process involving the upregulation of postsynaptic AMPA receptors (**GRIA1**, **GRIA4**) whose clustering is controlled by **PICK1** (Table 3). **BDNF**, which is released by NMDA receptor activation, plays an important role in this feed-forward increase in synaptic sensitivity via its multiple effects on glutamate release, and the control of the phosphorylation and expression of glutamate receptors and postsynaptic scaffold proteins (see Table 6). LTP is accompanied by increased postsynaptic dendritic spine development (Yuste and Bonhoeffer, 2001) which is NMDA receptor dependent (Collin et al., 1997; Toni et al., 1999).

A number of genes associated with schizophrenia (**ALK**, **CHL1**, **CHN2**, **DPYSL2**, **DISC1**, **FEZ1**, **MAG**, **NTNG1**, **NTNG2**, **PLXNA2**, **RTN4**, **RTN4R**) are specifically involved in the control of neurite/dendrite formation or synaptic plasticity (See Table 5). Growth factors (**BDNF**, **CNTF**, **EGF**) and their PI3kinase signalling pathway (**PIK3C3**, **PIP5K2A**, **AKT1**,) also regulate this aspect of neuronal morphology (See Table 6).The **AKT1** pathway is also activated by NMDA receptor stimulation and **AKT1** phosphorylates NMDA receptors, potentiating their effects (Sanchez-Perez et al., 2006).

Many genes associated with schizophrenia either code for important oligodendrocyte constituents (**CNP**, **MAG**, **MOG** and **PLP1**) or regulate oligodendrocyte viability (**CNTF**, **NRG1**, **ERBB4**, **NOTCH4**, **PAX6**, and **QK1**) (See Table 7). Both glutamate and dopamine also kill oligodendrocytes via receptor-independent mechanisms, the former via inhibition of the transport of the glutathione precursor cysteine by **SLC1A2** (Rosin et al., 2004) and the latter by a mechanism accompanied by glutathione depletion and likely involving the generation of dopamine-derived oxidation products (quinones) (Khorchid et al., 2002). NMDA receptor stimulation has been shown to release the potent antioxidant reduced glutathione (Wallin et al., 1999), which protects oligodendrocytes from diverse toxic insults (see Table 7). A number of genes involved in dopamine metabolism storage, release or uptake (**ADH1B**, **ALDH3B1**, **CHGB**, **COMT**, **MAOA**, **KCNN3**, **TH**, **SLC6A3**) have been associated with schizophrenia (Table 8). Both **DRD2** and **DRD3** dopamine receptors are involved in oligodendrocyte development and their stimulation protects oligodendrocytes from glutamate and oxidative stress related toxicity (See Table 7). **IL1B**, **LTA**, **NOS1**, **TNFA**, **PLA2G4** and **TP53** are also involved in oligodendrocyte toxicity and **BDNF**, **EGF** or **NTF3**, as well as **CNR1** or **GRM5** receptor agonists, protect oligodendrocytes against various insults (Table 7). The class II major histocompatibility complex, **HLA-DRB1**, recognizes antigenic peptides derived from the oligodendrocyte protein **MOG** and also recognises peptides derived from the influenza and Rubella viruses and from the spirochete Borrelia burgdorferi which causes Lyme disease carried by Ixodes ticks (see Table 7 for references). Influenza, Rubella and Borrelia burgdorferi have been implicated in schizophrenia (see Introduction) and this molecular mimicry suggests that these environmental influences may well affect oligodendrocyte function.

The oxidation of dopamine to cytotoxic quinones can occur spontaneously. It is also enzymatically driven by **PTGS2**, **TYR** or **S100B** (see Table 9). Quinone protection mechanisms are represented by **GSTM1**, **NQO2** and the glutamate/cysteine transporter, **SLC1A2**, as well as by **COMT** (See Table 9).

Serotonin system related genes are represented in Table 10 and miscellaneous genes annotated in Table 11. Many of these, and other gene products, although not primarily concerned with glutamate transmission, dendrite development or oligodendrocyte function nevertheless do affect these parameters as shown in the last lines of Table 2 (Gene products affecting glutamate release), Table 3 (Gene products affecting NMDA receptors or scaffold proteins), Table 5 (Gene products affecting neuritogenesis) and Table 7 (Gene products affecting oligodendrocyte function).

The classification of these genes by family and their organisation into a signaling cascade implicated in the process of long-term potentiation is illustrated in Fig. 1. A summary of the various interactions between the protein products of some of these genes is illustrated in Fig. 2.

4. Discussion

Two problems need to be addressed before discussing the significance of this analysis; the problems of replicability and confirmation in association studies, and the fact that genes are chosen for study because of prevalent theories in schizophrenia (selection bias). It should also be noted that the association of some of these genes with schizophrenia, particularly when not yet replicated or supported by other functional or expression data is tenuous (DeLisi and Faraone, 2006).

4.1. Heterogeneity in association studies

A widely held view, given the enormous problems of replicability in genetic association studies, is that many of these report false positives because of problems in

statistical power and replicability, or because of recombination effects in which a nearby linked susceptibility gene may influence the association of another with the disease. Independent validation of individual association studies together with functional characterisation is of paramount importance, and lacking in many cases (DeLisi and Faraone, 2006; Hirschhorn et al., 2002). There is however a precedent that may provide a physiological explanation for some of the heterogeneity in association studies. Bladder cancer is also a multigenic disease involving multiple chromosomal loci (Yanagida et al., 2001). A recent study measured the association of 44-cell cycle and DNA-repair pathway polymorphic genes, only three of which were significantly associated with this disease, when assessed individually (Wu et al., 2006). However, an increasing number of polymorphisms, in different genes, sequentially increased the risk of developing the disease. Within the DNA repair pathway, for 4 or more polymorphic genes, each additional adverse allele (including those not individually associated with the disease) was associated with a 1.21-fold progressive increase in risk. In the combined DNA repair and cell cycle pathways the integrative effects of almost half of the 44 polymorphic genes influenced the eventual risk outcome. In other words, the disease was more closely associated with the integrative effects of a number of polymorphic genes within a relevant physiological pathway, than with a variant in any particular gene.

Most of the association studies in schizophrenia relate to single genes. As described by Owen, "…the mode of transmission is complex and probably reflects oligogenic inheritance against a polygenic background" (Owen, 2005). This polygenic background likely includes other polymorphic genes able to influence the pathology of schizophrenia.

Several studies have shown that synergistic effects exist between polymorphic genes and their effect on schizophrenia susceptibility. For example, the association of the neuregulin receptor **ERBB4** with schizophrenia may be conditioned by a concomitant polymorphism in the neuregulin gene, **NRG1** (Norton et al., 2005). Such reinforcing effects have also been observed for interactions between **DAO/DAOA** (Chumakov et al., 2002), **GRIN1/GRIN2B** (Qin et al., 2005), **TPH/SLC6A4** (Chotai et al., 2005) **EGF/TNFA** (Kampman et al., 2005) and **CLDN5/PLA2G4A** (Wei and Hemmings, 2005). Environmental factors may also affect genetic influences. For example, a Chinese study has shown that the association of **APOE** with schizophrenia was modified by date of birth and restricted to individuals born during times of famine (Liu et al., 2003). The recognition of **MOG** (Weissert et al., 2002), influenza (Hennecke and Wiley, 2002; Wedderburn et al., 1995), rubella (Nepom et al., 1997), and Lyme disease pathogen proteins (Steere et al., 2003) by **HLA-DRB1** provides another example of a potential gene-environment interaction that is likely to influence oligodendrocyte viability.

The integrative effects observed in the bladder cancer study are likely to prevail when the candidate susceptibility genes belong to the same pathological pathway or share the same function, as is manifestly the case in schizophrenia. Association studies along the lines of those performed in bladder cancer would evidently help to resolve these complex issues.

4.2. Selection bias

The clustering of these genes into families related to schizophrenia pathology has obviously been affected by prevalent theories in the field.[1] However, the majority of the genes listed in Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11 (all but 16, see website (Carter, 2006)) are also located within chromosomal regions associated with schizophrenia in microsatellite marker studies and this was often a guiding factor in their choice for association analysis.

It is important to note that gene expression and other functional studies tend to support an implication of many of these genes in the pathology of schizophrenia (see website for individual expression changes (Carter, 2006)). Genes whose implication is supported by association in 3 or more studies, by linkage studies suggesting an involvement of their chromosomal region and by expression or functional studies include **AKT1**, **BNDF**, **CAPON**, **CHRNA7**, **COMT**, **DAO**, **DAOA**, **DISC1**, **DPYSL2**, **DRD2**, **DRD3**, **DRD4**, **DTNNP1**, **GRIN1**, **GRIN2B**, **GRM3**, **HLA-DRB1**, **HTR2A**, **IL1RN**, **MTHFR**, **NOS1**, **NRG1**, **PLA2G4A**,

[1] **Selection bias**: A number of important susceptibility candidates, including **DAO** and **DAOA** (Chumakov et al., 2002), **DISC1** (Millar et al., 2000), **DTNBP1** (Straub et al., 2002), and **NRG1** (Stefansson et al., 2002) were initially identified as schizophrenia susceptibility genes from chromosome mapping studies. **CLDN5**, **COMT**, **PCQAP**, **PRODH**, **RTN4R**, **SNAP29**, **UFD1L**, **ZDHHC8**, and **ZNF74** are all located on chromosome 22q11 whose microdeletion is associated with a variety of developmental (Velo-cardio-facial syndrome, Di George syndrome) and psychiatric problems. 30% of adults with this deletion develop psychosis (Williams and Owen, 2004). The selection of these genes as susceptibility candidates is, to a certain extent, untrammelled by functional hypotheses, as is the selection of genes based on observations of chromosomal translocations (**NAALAD2**, **GRM5**, **NPAS3**, **TYR**, **B3GAT1**, **PDE4B**) and individual gene deletions (**GSTM1**).

PRODH, **RGS4**, **SLC6A4**, **SYN2**, **TH** and **TNFA**. Expression changes in schizophrenia have been observed for many others (see website) (Carter, 2006). Dysfunction in these gene categories is also generally supported by microarray and proteomics studies showing marked expression changes in presynaptic and postsynaptic elements related to glutamatergic transmission (Mirnics et al., 2000; Vawter et al., 2001), in genes related to neuritogenesis (Altar et al., 2005), in oligodendrocyte and myelin related constituents (Hakak et al., 2001; Katsel et al., 2005b; Sugai et al., 2004) (Hakak et al., 2001; Katsel et al., 2005a) in astrocyte and growth factor related genes (Sugai et al., 2004) and in components of glutathione and oxidative stress related pathways (Iwamoto et al., 2005; Prabakaran et al., 2004). Thus, despite the heterogeneity in association studies, converging expression and functional data support an implication for most of these genes or gene products in the disease process.

5. Physiological implications

This analysis suggests that genes associated with schizophrenia tend to cluster in families that can be related to some of the key pathological processes of this disease (glutamatergic and dopaminergic dysfunction, synaptic plasticity, oligodendrocyte cell loss and oxidative stress). As illustrated in the Results section and Fig. 1, a large number of these genes converge on a glutamatergic pathway involved in the consolidation of memory (long-term potentiation) in which glutamate, acting via NMDA receptors, promotes increases in synaptic strength involving a remodelling of the postsynaptic receptor profile and associated plastic dendritic changes (Bashir et al., 1991; Davies et al., 1989; Shi et al., 1999). NMDA receptor activation also releases a potent antioxidant, reduced glutathione (Wallin et al., 1999), which protects developing oligodendrocytes from diverse toxic insults, including those produced by dopamine, glutamate, AMPA receptor stimulation and **TNFA** (Khorchid et al., 2002; Lee et al., 2004; Richter-Landsberg and Vollgraf, 1998). Hypofunction of this signaling cascade could well lead to the impairments in the working memory functions of the prefrontal cortex that are a feature of schizophrenia (Goldman-Rakic and Selemon, 1997) and might also be able to influence glutathione function and oxidative stress. Glutathione levels are indeed reduced in the schizophrenic brain in life (Do et al., 2000). Developing oligodendrocytes are particularly sensitive to glutathione depletion (Back et al., 1998). Nitric oxide, a factor released by NMDA receptor stimulation, can exert toxic effects on oligoendrocytes but is able to protect developing oligodendrocytes from the effects of glutathione depletion (Rosenberg et al., 1999). Although oxidative stress might be expected to affect many cell types, it is tempting to suggest that the effects of NMDA receptor hypofunction on the NO/glutathione system and the abundance of susceptibility candidates related to the control of oligodendrocyte viability and function may combine to provide a means of dictating the vulnerability of this cell population.

Of the many genes associated with schizophrenia, only a few are now considered as serious susceptibility candidates. Recent reviews have listed **COMT**, **DAO**, **DISC1**, **DTNBP1**, **GRM3**, **NRG1** and **RGS4** as strong (but not universally agreed) risk factors, and the convergence of these genes on common physiological processes has already been discussed (Harrison and Owen, 2003; Harrison and Weinberger, 2005). This convergence appears to apply to a multitude of genes associated with schizophrenia.

In a complex system disease, with many different pathological features and endophenotypes, it is possible that several gene defects may be necessary to induce or influence the diverse aspects of the full-blown pathology and symptomatology of the disease. Thus, the fact that the various gene candidates cluster in families related to a number of different pathological processes in schizophrenia has important implications for association studies in this field.

It has already been shown that certain of these gene variants are related to specific endophenotypes within the disease (For review see (Cannon, 2005)). For example the high activity Val/Met **COMT** polymorphism has been related to prefrontal cognitive disturbances (Egan et al., 2001), P300 deficits (Gallinat et al., 2003) or eye movement disturbances (Rybakowski et al., 2002). One might presume that the genes involved in specific aspects of oxidative stress, oligodendrocyte function and plasticity might also be related to their equivalent sub-pathologies and corresponding endophenotypes in schizophrenia.

It is interesting that some of the major susceptibility candidates are able to affect many of these processes. For example, **NRG1** inhibits NMDA receptor function (Gu et al., 2005), induces neurite extension in hippocampal neurones (Gerecke et al., 2004), promotes oligodendrocyte growth (Flores et al., 2000), releases striatal dopamine when injected supra-nigrally (Yurek et al., 2004), and protects PC12 cells from H_2O_2 induced cell death (Goldshmit et al., 2001). **COMT** regulates dopamine metabolism but is also an important enzyme involved in quinone detoxification

(Zhu, 2004). Activation of this enzyme in astrocytes also increases the synthesis and release of the NMDA receptor agonist homocysteine, derived from the methylating **COMT** substrate *S*-adenosyl methionine (Huang et al., 2005).

The function of **DISC1** remains to be fully characterised, but it binds to components of the glutamate receptor scaffold (Millar et al., 2003) and to **FEZ1** which controls neurite outgrowth (Miyoshi et al., 2003). A further binding partner, ATF5 (Morris et al., 2003), controls astrocyte and oligodendrocyte development (Angelastro et al., 2005; Mason et al., 2005) while another, ATF4 (Morris et al., 2003), regulates the transcription of glutathione related genes and controls the ability of cells to resist oxidative stress (Harding et al., 2003). ATF4 binds to nrf2 (NFE2L2) (He et al., 2001), a key transcription factor regulating glutathione and quinone-related genes, including **GSTM1** and **NQO2**. NFE2L2 which is activated by oxidative stress, quinones and nitric oxide (cf, **SOD2**, **PTGS2**, **TYR**, **S100B**), also controls the transcription of **BDNF**, **CHGB**, **GABBR1**, **HMBS**, **PTGS2** and **SYN2** (Lee et al., 2003a,b; Yoo et al., 1993). **DISC1** thus appears to be a tantalising, but so far theoretical, link between the glutamate system and many other processes implicated in schizophrenia. This potential transduction hub, as well as other links between NMDA receptor signaling and oligodendrocyte function, clearly merits investigation.

Certain genes may thus be able to affect many relevant underlying pathological processes, while others (for example those concerned only with glutamate release) may exert more specific and selective effects. These factors are likely to contribute to the importance and replicability of each polymorphism in association studies.

5.1. Protein/protein interactions (see Fig. 2)

Many of these gene products form micro complexes involved in very specific processes. For example, at presynaptic sites, **CAPON** binds to the synapsins SYN1, **SYN2** and **SYN3** leading to the formation of a ternary complex between **NOS1**, SYN1 and **CAPON** that is involved in the regulation of glutamate release by nitric oxide (Jaffrey et al., 2002). Nitric oxide modifies glutamate release via the *S*-nitrosylation of synaptic SNARE proteins including **STX1A** (Di Stasi et al., 2002). Many components of the postsynaptic receptor scaffold complex (**APC**, **CAPON**, **DLG2**, **GRIN1**, **GRIN2A**, **GRIN2B**, **ERBB4**, **NOS1**) are all interconnected via diverse protein/protein interactions. The D1 dopamine receptor DRD1 also binds to the NMDA receptor subunits **GRIN1** and **GRIN2A** and controls both **NMDA** receptor-mediated currents and phosphoinositide signaling (Lee et al., 2002). These interactions may play a key role in the disruption of DRD1/NMDA receptor signaling in the frontal cortex (Yang and Chen, 2005)(see Introduction). **DISC1** also binds to other proteins whose genes have been associated with schizophrenia (**FEZ1**, **MLC1** and **PDE4B**) suggesting a certain degree of functional convergence at this level. **PTGS2**, **S100B** and **SOD2** all bind to the tumor suppressor **TP53**, which also controls **TYR** expression (See Table 9 for references). These and other protein/protein interactions are cited in the website tables and illustrated in Fig. 2. The effects of defects in genes controlling the same microprocesses would again be expected to be integrative, both at the functional and genetic level, and the same conditional effects of various polymorphisms within these networks might be expected to apply. An analysis of protein/protein interactions in the human proteome has also noted that proteins implicated in inherited disorders tend to interact with proteins implicated in similar types of disorders, suggesting the existence of disease subnetworks (Gandhi et al., 2006). This functional convergence and interaction between protein products may also exist within a particular multigenic disease.

6. Relevance to current and developing therapies

The interest in glutamatergic hypofunction in schizophrenia is related to the ability of NMDA receptor channel blockers (ketamine, phencyclidine) to produce many of the symptoms of psychosis and many developing therapies are targeted towards increasing NMDA receptor function. There is some evidence that this approach may be effective. For review see (Coyle and Tsai, 2004). It is to a certain extent possible to rationalise the effects of neuroleptics in terms of their indirect effects upon glutamatergic function and to interactions between dopaminergic and glutamatergic systems at multiple levels. For example **DRD2** receptor activation inhibits glutamate release in subcortical areas (Bamford et al., 2004; Kalivas and Duffy, 1997) and inhibits the effects of NMDA receptor activation in the hippocampus (Wang et al., 2003). It has been shown that chronic treatment with haloperidol or clozapine in rats increases the number of NMDA receptors labelled with [^{3}H]CGP 39653 in different cortical areas. Chronic haloperidol treatment in rats has also been shown to significantly increase the number of dendritic spines in the striatum as well as the number of synaptic boutons (Kerns et al., 1992). Many other reported effects are

beyond the scope of this review. Interestingly, the chronic administration of the atypical neuroleptics olanzapine and risperidone, but not haloperidol, increases the expression of **DISC1** in the frontal cortex in mice (Chiba et al., 2006) suggesting that these drugs may target this important transduction hub.

No drugs in current use appear to target either the problems of oligodendrocyte viability or of glutathione-related oxidative stress in schizophrenia, an area that perhaps requires further research. It is of note that the oligodendrocyte cell loss and demyelination produced in rat pups whose mothers were treated with the endotoxin lipopolysaccharide during pregnancy can be prevented by the glutathione precursor *N*-acetylcysteine (Paintlia et al., 2004).

7. Conclusion

Genes implicated in schizophrenia cluster in families related to key pathological processes and can be organised into a clearly defined signaling cascade related to NMDA receptor-dependent long-term potentiation. Multiple interactions between their protein products suggest a complex integrated network whose dysfunction may well underpin the pathology of schizophrenia. Certain major susceptibility candidates appear to be related to many of the underlying pathological processes. None of these polymorphic genes, in isolation, can be considered as a definable susceptibility gene for all cases of schizophrenia, and many individual polymorphisms may also exist in the normal population at similar frequencies. However, because of the overall functional convergence, the risk-generating effects of each polymorphism may be conditioned by concomitant variants in genes coding for their binding partners, transcriptional relatives or components of the same signaling cascade. The association of many genes may thus be restricted to subsets of patients with polymorphisms in related genes, whose integrative effects combine to produce the disease (See (Wu et al., 2006)). Such factors may well contribute to the heterogeneity in association studies, which may be a reflection of the complexity of the underlying pathological pathway(s). Genetic association studies may in fact etch out the underlying pathological pathways, a conclusion that has far-reaching implications for a number of diseases of multigenic origin.

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References

Altar, C.A., Jurata, L.W., Charles, V., Lemire, A., Liu, P., Bukhman, Y., Young, T.A., Bullard, J., Yokoe, H., Webster, M.J., Knable, M. B., Brockman, J.A., 2005. Deficient hippocampal neuron expression of proteasome, ubiquitin, and mitochondrial genes in multiple schizophrenia cohorts. Biol. Psychiatry 58, 85–96.

Angelastro, J.M., Mason, J.L., Ignatova, T.N., Kukekov, V.G., Stengren, G.B., Goldman, J.E., Greene, L.A., 2005. Down-regulation of activating transcription factor 5 is required for differentiation of neural progenitor cells into astrocytes. J. Neurosci. 25, 3889–3899.

Back, S.A., Gan, X., Li, Y., Rosenberg, P.A., Volpe, J.J., 1998. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. J. Neurosci. 18, 6241–6253.

Bamford, N.S., Zhang, H., Schmitz, Y., Wu, N.P., Cepeda, C., Levine, M.S., Schmauss, C., Zakharenko, S.S., Zablow, L., Sulzer, D., 2004. Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals. Neuron 42, 653–663.

Bashir, Z.I., Alford, S., Davies, S.N., Randall, A.D., Collingridge, G.L., 1991. Long-term potentiation of NMDA receptor-mediated synaptic transmission in the hippocampus. Nature 349, 156–158.

Becker, K.G., Barnes, K.C., Bright, T.J., Wang, S.A., 2004. The genetic association database. Nat. Genet. 36, 431–432.

Black, J.E., Kodish, I.M., Grossman, A.W., Klintsova, A.Y., Orlovskaya, D., Vostrikov, V., Uranova, N., Greenough, W.T., 2004. Pathology of layer V pyramidal neurons in the prefrontal cortex of patients with schizophrenia. Am. J. Psychiatry 161, 742–744.

Brenman, J.E., Bredt, D.S., 1997. Synaptic signaling by nitric oxide. Curr. Opin. Neurobiol. 7, 374–378.

Brown Jr., J.S., 1994. Geographic correlation of schizophrenia to ticks and tick-borne encephalitis. Schizophr. Bull. 20, 755–775.

Brown, A.S., 2006. Prenatal infection as a risk factor for schizophrenia. Schizophr. Bull.

Calakos, N., Scheller, R.H., 1996. Synaptic vesicle biogenesis, docking, and fusion: a molecular description. Physiol. Rev. 76, 1–29.

Cannon, T.D., 2005. The inheritance of intermediate phenotypes for schizophrenia. Curr. Opin. Psychiatry 18, 135–140.

Carlsson, A., Waters, N., Hansson, O., 1994. Neurotransmitter aberrations in schizophrenia: new findings. In: Fog, R., Gerlach, R., Hemmingen, R. (Eds.), Schizophrenia, Alfred Benzon Symposium, vol. 38. Munksgaard, Copenhagen.

Carter, C.J., 2006. Polygenic signaling pathways. http://www.polygenicpathways.co.uk. Website. Ref Type: Electronic Citation.

Chen, A., Muzzio, I.A., Malleret, G., Bartsch, D., Verbitsky, M., Pavlidis, P., Yonan, A.L., Vronskaya, S., Grody, M.B., Cepeda, I., Gilliam, T.C., Kandel, E.R., 2003. Inducible enhancement of

memory storage and synaptic plasticity in transgenic mice expressing an inhibitor of ATF4 (CREB-2) and C/EBP proteins. Neuron 39, 655–669.

Chiba, S., Hashimoto, R., Hattori, S., Yohda, M., Lipska, B., Weinberger, D.R., Kunugi, H., 2006. Effect of antipsychotic drugs on DISC1 and dysbindin expression in mouse frontal cortex and hippocampus. J. Neural Transm.

Chotai, J., Serretti, A., Lorenzi, C., 2005. Interaction between the tryptophan hydroxylase gene and the serotonin transporter gene in schizophrenia but not in bipolar or unipolar affective disorders. Neuropsychobiology 51, 3–9.

Chumakov, I., Blumenfeld, M., Guerassimenko, O., Cavarec, L., Palicio, M., Abderrahim, H., Bougueleret, L., Barry, C., Tanaka, H., La Rosa, P., Puech, A., Tahri, N., Cohen-Akenine, A., Delabrosse, S., Lissarrague, S., Picard, F.P., Maurice, K., Essioux, L., Millasseau, P., Grel, P., Debailleul, V., Simon, A.M., Caterina, D., Dufaure, I., Malekzadeh, K., Belova, M., Luan, J.J., Bouillot, M., Sambucy, J.L., Primas, G., Saumier, M., Boubkiri, N., Martin-Saumier, S., Nasroune, M., Peixoto, H., Delaye, A., Pinchot, V., Bastucci, M., Guillou, S., Chevillon, M., Sainz-Fuertes, R., Meguenni, S., Aurich-Costa, J., Cherif, D., Gimalac, A., Van Duijn, C., Gauvreau, D., Ouellette, G., Fortier, I., Raelson, J., Sherbatich, T., Riazanskaia, N., Rogaev, E., Raeymaekers, P., Aerssens, J., Konings, F., Luyten, W., Macciardi, F., Sham, P.C., Straub, R.E., Weinberger, D.R., Cohen, N., Cohen, D., Ouelette, G., Realson, J., 2002. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 99, 13675–13680.

Collin, C., Miyaguchi, K., Segal, M., 1997. Dendritic spine density and LTP induction in cultured hippocampal slices. J. Neurophysiol. 77, 1614–1623.

Coyle, J.T., Tsai, G., 2004. The NMDA receptor glycine modulatory site: a therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. Psychopharmacology (Berl) 174, 32–38.

Davis, J.O., Bracha, H.S., 1996. Famine and schizophrenia: first-trimester malnutrition or second-trimester beriberi. Biol. Psychiatry 40, 1–3.

Davies, S.N., Lester, R.A., Reymann, K.G., Collingridge, G.L., 1989. Temporally distinct pre- and post-synaptic mechanisms maintain long-term potentiation. Nature 338, 500–503.

DeLisi, L.E., Faraone, S.V., 2006. When is a "positive" association truly a "positive" in psychiatric genetics? Am. J. Med. Genet. 141, 319–322.

Di Stasi, A.M., Mallozzi, C., Macchia, G., Maura, G., Petrucci, T.C., Minetti, M., 2002. Peroxynitrite affects exocytosis and SNARE complex formation and induces tyrosine nitration of synaptic proteins. J. Neurochem. 82, 420–429.

Do, K.Q., Trabesinger, A.H., Kirsten-Kruger, M., Lauer, C.J., Dydak, U., Hell, D., Holsboer, F., Boesiger, P., Cuenod, M., 2000. Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur. J. Neurosci. 12, 3721–3728.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R., 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 98, 6917–6922.

Feliciello, A., Cardone, L., Garbi, C., Ginsberg, M.D., Varrone, S., Rubin, C.S., Avvedimento, E.V., Gottesman, M.E., 1999. Yotiao protein, a ligand for the NMDA receptor, binds and targets cAMP-dependent protein kinase II(1). FEBS Lett. 464, 174–178.

Flores, A.I., Mallon, B.S., Matsui, T., Ogawa, W., Rosenzweig, A., Okamoto, T., Macklin, W.B., 2000. Akt-mediated survival of oligodendrocytes induced by neuregulins. J. Neurosci. 20, 7622–7630.

Flynn, S.W., Lang, D.J., Mackay, A.L., Goghari, V., Vavasour, I.M., Whittall, K.P., Smith, G.N., Arango, V., Mann, J.J., Dwork, A.J., Falkai, P., Honer, W.G., 2003. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. Mol. Psychiatry 8, 811–820.

Gallinat, J., Bajbouj, M., Sander, T., Schlattmann, P., Xu, K., Ferro, E.F., Goldman, D., Winterer, G., 2003. Association of the G1947A COMT (Val(108/158)Met) gene polymorphism with prefrontal P300 during information processing. Biol. Psychiatry 54, 40–48.

Gandhi, T.K., Zhong, J., Mathivanan, S., Karthick, L., Chandrika, K.N., Mohan, S.S., Sharma, S., Pinkert, S., Nagaraju, S., Periaswamy, B., Mishra, G., Nandakumar, K., Shen, B., Deshpande, N., Nayak, R., Sarker, M., Boeke, J.D., Parmigiani, G., Schultz, J., Bader, J.S., Pandey, A., 2006. Analysis of the human protein interactome and comparison with yeast, worm and fly interaction datasets. Nat. Genet. 38, 285–293.

Garey, L.J., Ong, W.Y., Patel, T.S., Kanani, M., Davis, A., Mortimer, A.M., Barnes, T.R., Hirsch, S.R., 1998. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J. Neurol. Neurosurg. Psychiatry 65, 446–453.

Gerecke, K.M., Wyss, J.M., Carroll, S.L., 2004. Neuregulin-1beta induces neurite extension and arborization in cultured hippocampal neurons. Mol. Cell. Neurosci. 27, 379–393.

Glantz, L.A., Lewis, D.A., 2000. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch. Gen. Psychiatry 57, 65–73.

Goldman-Rakic, P.S., Selemon, L.D., 1997. Functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophr. Bull. 23, 437–458.

Goldman-Rakic, P.S., Castner, S.A., Svensson, T.H., Siever, L.J., Williams, G.V., 2004. Targeting the dopamine D(1) receptor in schizophrenia: insights for cognitive dysfunction. Psychopharmacology (Berl) 174, 3–16.

Goldshmit, Y., Erlich, S., Pinkas-Kramarski, R., 2001. Neuregulin rescues PC12-ErbB4 cells from cell death induced by H(2)O(2). Regulation of reactive oxygen species levels by phosphatidylinositol 3-kinase. J. Biol. Chem. 276, 46379–46385.

Gu, Z., Jiang, Q., Fu, A.K., Ip, N.Y., Yan, Z., 2005. Regulation of NMDA receptors by neuregulin signaling in prefrontal cortex. J. Neurosci. 25, 4974–4984.

Hakak, Y., Walker, J.R., Li, C., Wong, W.H., Davis, K.L., Buxbaum, J. D., Haroutunian, V., Fienberg, A.A., 2001. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 98, 4746–4751.

Harding, H.P., Zhang, Y., Zeng, H., Novoa, I., Lu, P.D., Calfon, M., Sadri, N., Yun, C., Popko, B., Paules, R., Stojdl, D.F., Bell, J.C., Hettmann, T., Leiden, J.M., Ron, D., 2003. An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. Mol. Cell 11, 619–633.

Harrison, P.J., Owen, M.J., 2003. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 361, 417–419.

Harrison, P.J., Weinberger, D.R., 2005. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry 10, 40–68.

He, C.H., Gong, P., Hu, B., Stewart, D., Choi, M.E., Choi, A.M., Alam, J., 2001. Identification of activating transcription factor 4

(ATF4) as an Nrf2-interacting protein. Implication for heme oxygenase-1 gene regulation. J. Biol. Chem. 276, 20858–20865.
Hennecke, J., Wiley, D.C., 2002. Structure of a complex of the human alpha/beta T cell receptor (TCR) HA1.7, influenza hemagglutinin peptide, and major histocompatibility complex class II molecule, HLA-DR4 (DRA*0101 and DRB1*0401): insight into TCR cross-restriction and alloreactivity. J. Exp. Med. 195, 571–581.
Hirschhorn, J.N., Lohmueller, K., Byrne, E., Hirschhorn, K., 2002. A comprehensive review of genetic association studies. Genet. Med. 4, 45–61.
Hof, P.R., Haroutunian, V., Copland, C., Davis, K.L., Buxbaum, J.D., 2002. Molecular and cellular evidence for an oligodendrocyte abnormality in schizophrenia. Neurochem. Res. 27, 1193–1200.
Hof, P.R., Haroutunian, V., Friedrich Jr., V.L., Byne, W., Buitron, C., Perl, D.P., Davis, K.L., 2003. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. Biol. Psychiatry 53, 1075–1085.
Huang, G., Dragan, M., Freeman, D., Wilson, J.X., 2005. Activation of catechol-*O*-methyltransferase in astrocytes stimulates homocysteine synthesis and export to neurons. Glia 51, 47–55.
Iwamoto, K., Bundo, M., Kato, T., 2005. Altered expression of mitochondria-related genes in postmortem brains of patients with bipolar disorder or schizophrenia, as revealed by large-scale DNA microarray analysis. Hum. Mol. Genet. 14, 241–253.
Jaffrey, S.R., Snowman, A.M., Eliasson, M.J., Cohen, N.A., Snyder, S.H., 1998. CAPON: a protein associated with neuronal nitric oxide synthase that regulates its interactions with PSD95. Neuron 20, 115–124.
Jaffrey, S.R., Benfenati, F., Snowman, A.M., Czernik, A.J., Snyder, S.H., 2002. Neuronal nitric-oxide synthase localization mediated by a ternary complex with synapsin and CAPON. Proc. Natl. Acad. Sci. U. S. A. 99, 3199–3204.
Johnstone, E.C., Crow, T.J., Frith, C.D., Husband, J., Kreel, L., 1976. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2, 924–926.
Kalivas, P.W., Duffy, P., 1997. Dopamine regulation of extracellular glutamate in the nucleus accumbens. Brain Res. 761, 173–177.
Kampman, O., Anttila, S., Illi, A., Mattila, K.M., Rontu, R., Leinonen, E., Lehtimaki, T., 2005. Interaction of tumor necrosis alpha-G308A and epidermal growth factor gene polymorphisms in early-onset schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 255, 279–283.
Katsel, P., Davis, K.L., Haroutunian, V., 2005a. Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: a gene ontology study. Schizophr. Res.
Katsel, P., Davis, K.L., Haroutunian, V., 2005b. Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: a gene ontology study. Schizophr. Res.
Kerns, J.M., Sierens, D.K., Kao, L.C., Klawans, H.L., Carvey, P.M., 1992. Synaptic plasticity in the rat striatum following chronic haloperidol treatment. Clin Neuropharmacol 15, 488–500.
Khorchid, A., Fragoso, G., Shore, G., Almazan, G., 2002. Catecholamine-induced oligodendrocyte cell death in culture is developmentally regulated and involves free radical generation and differential activation of caspase-3. Glia 40, 283–299.
Knable, M.B., Torrey, E.F., Webster, M.J., Bartko, J.J., 2001. Multivariate analysis of prefrontal cortical data from the Stanley Foundation Neuropathology Consortium. Brain Res. Bull. 55, 651–659.
Kung, L., Conley, R., Chute, D.J., Smialek, J., Roberts, R.C., 1998. Synaptic changes in the striatum of schizophrenic cases: a controlled postmortem ultrastructural study. Synapse 28, 125–139.
Laruelle, M., Kegeles, L.S., Abi-Dargham, A., 2003. Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. Ann. N. Y. Acad. Sci. 1003, 138–158.
Lee, F.J., Xue, S., Pei, L., Vukusic, B., Chery, N., Wang, Y., Wang, Y.T., Niznik, H.B., Yu, X.M., Liu, F., 2002. Dual regulation of NMDA receptor functions by direct protein–protein interactions with the dopamine D1 receptor. Cell 111, 219–230.
Lee, J.M., Calkins, M.J., Chan, K., Kan, Y.W., Johnson, J.A., 2003a. Identification of the NF-E2-related factor-2-dependent genes conferring protection against oxidative stress in primary cortical astrocytes using oligonucleotide microarray analysis. J. Biol. Chem. 278, 12029–12038.
Lee, J.M., Shih, A.Y., Murphy, T.H., Johnson, J.A., 2003b. NF-E2-related factor-2 mediates neuroprotection against mitochondrial complex I inhibitors and increased concentrations of intracellular calcium in primary cortical neurons. J. Biol. Chem. 278, 37948–37956.
Lee, J.T., Xu, J., Lee, J.M., Ku, G., Han, X., Yang, D.I., Chen, S., Hsu, C.Y., 2004. Amyloid-{beta} peptide induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide pathway. J. Cell Biol. 164, 123–131.
Lewis, D.A., Volk, D.W., Hashimoto, T., 2004. Selective alterations in prefrontal cortical GABA neurotransmission in schizophrenia: a novel target for the treatment of working memory dysfunction. Psychopharmacology (Berl) 174, 143–150.
Liu, W., Breen, G., Zhang, J., Li, S., Gu, N., Feng, G., Bai, S., Shen, T., Yu, A., Xue, H., St Clair, D., He, L., 2003. Association of APOE gene with schizophrenia in Chinese: a possible risk factor in times of malnutrition. Schizophr. Res. 62, 225–230.
Mahadik, S.P., Scheffer, R.E., 1996. Oxidative injury and potential use of antioxidants in schizophrenia. Prostaglandins Leukot. Essent. Fat. Acids 55, 45–54.
Mason, J.L., Angelastro, J.M., Ignatova, T.N., Kukekov, V.G., Lin, G., Greene, L.A., Goldman, J.E., 2005. ATF5 regulates the proliferation and differentiation of oligodendrocytes. Mol. Cell. Neurosci. 29, 372–380.
Millar, J.K., Wilson-Annan, J.C., Anderson, S., Christie, S., Taylor, M. S., Semple, C.A., Devon, R.S., Clair, D.M., Muir, W.J., Blackwood, D.H., Porteous, D.J., 2000. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum. Mol. Genet. 9, 1415–1423.
Millar, J.K., Christie, S., Porteous, D.J., 2003. Yeast two-hybrid screens implicate DISC1 in brain development and function. Biochem. Biophys. Res. Commun. 311, 1019–1025.
Mirnics, K., Middleton, F.A., Marquez, A., Lewis, D.A., Levitt, P., 2000. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. Neuron 28, 53–67.
Miyoshi, K., Honda, A., Baba, K., Taniguchi, M., Oono, K., Fujita, T., Kuroda, S., Katayama, T., Tohyama, M., 2003. Disrupted-in-schizophrenia 1, a candidate gene for schizophrenia, participates in neurite outgrowth. Mol. Psychiatry 8, 685–694.
Morris, J.A., Kandpal, G., Ma, L., Austin, C.P., 2003. DISC1 (Disrupted-In-Schizophrenia 1) is a centrosome-associated protein that interacts with MAP1A, MIPT3, ATF4/5 and NUDEL: regulation and loss of interaction with mutation. Hum. Mol. Genet. 12, 1591–1608.
Nepom, G.T., Domeier, M.E., Ou, D., Kovats, S., Mitchell, L.A., Tingle, A.J., 1997. Recognition of contiguous allele-specific peptide elements in the rubella virus E1 envelope protein. Vaccine 15, 648–652.
Norton, N., Moskvina, V., Morris, D.W., Bray, N.J., Zammit, S., Williams, N.M., Williams, H.J., Preece, A.C., Dwyer, S.,

Wilkinson, J.C., Spurlock, G., Kirov, G., Buckland, P., Waddington, J.L., Gill, M., Corvin, A.P., Owen, M.J., O'Donovan, M.C., 2005. Evidence that interaction between neuregulin 1 and its receptor erbB4 increases susceptibility to schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet.

Owen, M.J., 2005. Genomic approaches to schizophrenia. Clin. Ther. 27 (Suppl A), S2–S7.

Paintlia, M.K., Paintlia, A.S., Barbosa, E., Singh, I., Singh, A.K., 2004. *N*-acetylcysteine prevents endotoxin-induced degeneration of oligodendrocyte progenitors and hypomyelination in developing rat brain. J. Neurosci. Res. 78, 347–361.

Prabakaran, S., Swatton, J.E., Ryan, M.M., Huffaker, S.J., Huang, J.J., Griffin, J.L., Wayland, M., Freeman, T., Dudbridge, F., Lilley, K. S., Karp, N.A., Hester, S., Tkachev, D., Mimmack, M.L., Yolken, R.H., Webster, M.J., Torrey, E.F., Bahn, S., 2004. Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. Mol. Psychiatry 9, 684–697.

Qin, S., Zhao, X., Pan, Y., Liu, J., Feng, G., Fu, J., Bao, J., Zhang, Z., He, L., 2005. An association study of the *N*-methyl-D-aspartate receptor NR1 subunit gene (*GRIN1*) and NR2B subunit gene (*GRIN2B*) in schizophrenia with universal DNA microarray. Eur. J. Hum. Genet. 13, 807–814.

Rameau, G.A., Chiu, L.Y., Ziff, E.B., 2003. NMDA receptor regulation of nNOS phosphorylation and induction of neuron death. Neurobiol. Aging 24, 1123–1133.

Rapoport, J.L., Addington, A.M., Frangou, S., Psych, M.R., 2005. The neurodevelopmental model of schizophrenia: update 2005. Mol. Psychiatry.

Reddy, R.D., Yao, J.K., 1996. Free radical pathology in schizophrenia: a review. Prostaglandins Leukot. Essent. Fat. Acids 55, 33–43.

Richter-Landsberg, C., Vollgraf, U., 1998. Mode of cell injury and death after hydrogen peroxide exposure in cultured oligodendroglia cells. Exp. Cell Res. 244, 218–229.

Rosenberg, P.A., Li, Y., Ali, S., Altiok, N., Back, S.A., Volpe, J.J., 1999. Intracellular redox state determines whether nitric oxide is toxic or protective to rat oligodendrocytes in culture. J. Neurochem. 73, 476–484.

Rosin, C., Bates, T.E., Skaper, S.D., 2004. Excitatory amino acid induced oligodendrocyte cell death in vitro: receptor-dependent and -independent mechanisms. J. Neurochem. 90, 1173–1185.

Rosoklija, G., Toomayan, G., Ellis, S.P., Keilp, J., Mann, J.J., Latov, N., Hays, A.P., Dwork, A.J., 2000. Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: preliminary findings. Arch. Gen. Psychiatry 57, 349–356.

Rutkowski, D.T., Kaufman, R.J., 2003. All roads lead to ATF4. Dev. Cell 4, 442–444.

Rybakowski, J.K., Borkowska, A., Czerski, P.M., Hauser, J., 2002. Eye movement disturbances in schizophrenia and a polymorphism of catechol-*O*-methyltransferase gene. Psychiatry Res. 113, 49–57.

Sanchez-Perez, A.M., Llansola, M., Felipo, V., 2006. Modulation of NMDA receptors by AKT kinase. Neurochem. Int.

Selemon, L.D., Goldman-Rakic, P.S., 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol. Psychiatry 45, 17–25.

Shi, S.H., Hayashi, Y., Petralia, R.S., Zaman, S.H., Wenthold, R.J., Svoboda, K., Malinow, R., 1999. Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation. Science 284, 1811–1816.

Steere, A.C., Falk, B., Drouin, E.E., Baxter-Lowe, L.A., Hammer, J., Nepom, G.T., 2003. Binding of outer surface protein A and human lymphocyte function-associated antigen 1 peptides to HLA-DR molecules associated with antibiotic treatment-resistant Lyme arthritis. Arthritis Rheum. 48, 534–540.

Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T., Hjaltason, O., Birgisdottir, B., Jonsson, H., Gudnadottir, V.G., Gudmundsdottir, E., Bjornsson, A., Ingvarsson, B., Ingason, A., Sigfusson, S., Hardardottir, H., Harvey, R.P., Lai, D., Zhou, M., Brunner, D., Mutel, V., Gonzalo, A., Lemke, G., Sainz, J., Johannesson, G., Andresson, T., Gudbjartsson, D., Manolescu, A., Frigge, M.L., Gurney, M.E., Kong, A., Gulcher, J.R., Petursson, H., Stefansson, K., 2002. Neuregulin 1 and susceptibility to schizophrenia. Am. J. Hum. Genet. 71, 877–892.

Straub, R.E., Jiang, Y., MacLean, C.J., Ma, Y., Webb, B.T., Myakishev, M.V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B., Cesare, A.J., Gibberman, A., Wang, X., O'Neill, F. A., Walsh, D., Kendler, K.S., 2002. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am. J. Hum. Genet. 71, 337–348.

Sugai, T., Kawamura, M., Iritani, S., Araki, K., Makifuchi, T., Imai, C., Nakamura, R., Kakita, A., Takahashi, H., Nawa, H., 2004. Prefrontal abnormality of schizophrenia revealed by DNA microarray: impact on glial and neurotrophic gene expression. Ann. N. Y. Acad. Sci. 1025, 84–91.

Swiercz, J.M., Kuner, R., Offermanns, S., 2004. Plexin-B1/RhoGEF-mediated RhoA activation involves the receptor tyrosine kinase ErbB-2. J. Cell Biol. 165, 869–880.

Talukder, A.H., Vadlamudi, R., Mandal, M., Kumar, R., 2000. Heregulin induces expression, DNA binding activity, and transactivating functions of basic leucine zipper activating transcription factor 4. Cancer Res. 60, 276–281.

Toni, N., Buchs, P.A., Nikonenko, I., Bron, C.R., Muller, D., 1999. LTP promotes formation of multiple spine synapses between a single axon terminal and a dendrite. Nature 402, 421–425.

Uranova, N., Orlovskaya, D., Vikhreva, O., Zimina, I., Kolomeets, N., Vostrikov, V., Rachmanova, V., 2001. Electron microscopy of oligodendroglia in severe mental illness. Brain Res. Bull. 55, 597–610.

Uranova, N.A., Vostrikov, V.M., Orlovskaya, D.D., Rachmanova, V.I., 2004. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr. Res. 67, 269–275.

Vawter, M.P., Barrett, T., Cheadle, C., Sokolov, B.P., Wood III, W.H., Donovan, D.M., Webster, M., Freed, W.J., Becker, K.G., 2001. Application of cDNA microarrays to examine gene expression differences in schizophrenia. Brain Res. Bull. 55, 641–650.

Vostrikov, V.M., Uranova, N.A., Rakhmanova, V.I., Orlovskaia, D.D., 2004. Lowered oligodendroglial cell density in the prefrontal cortex in schizophrenia. Zh. Nevropatol. Psikhiatr. Im. S. S. Korsakova 104, 47–51.

Wain, H.M., Bruford, E.A., Lovering, R.C., Lush, M.J., Wright, M.W., Povey, S., 2002. Guidelines for human gene nomenclature. Genomics 79, 464–470.

Wallin, C., Weber, S.G., Sandberg, M., 1999. Glutathione efflux induced by NMDA and kainate: implications in neurotoxicity? J. Neurochem. 73, 1566–1572.

Wang, X., Zhong, P., Gu, Z., Yan, Z., 2003. Regulation of NMDA receptors by dopamine D4 signaling in prefrontal cortex. J. Neurosci. 23, 9852–9861.

Wechsler, A., Teichberg, V.I., 1998. Brain spectrin binding to the NMDA receptor is regulated by phosphorylation, calcium and calmodulin. EMBO J. 17, 3931–3939.

Wedderburn, L.R., Searle, S.J., Rees, A.R., Lamb, J.R., Owen, M.J., 1995. Mapping T cell recognition: the identification of a T cell receptor residue critical to the specific interaction with an influenza hemagglutinin peptide. Eur. J. Immunol. 25, 1654–1662.

Wei, J., Hemmings, G.P., 2005. A study of the combined effect of the CLDN5 locus and the genes for the phospholipid metabolism pathway in schizophrenia. Prostaglandins Leukot. Essent. Fat. Acids.

Weissert, R., Kuhle, J., de Graaf, K.L., Wienhold, W., Herrmann, M.M., Muller, C., Forsthuber, T.G., Wiesmuller, K.H., Melms, A., 2002. High immunogenicity of intracellular myelin oligodendrocyte glycoprotein epitopes. J. Immunol. 169, 548–556.

White, J.H., McIllhinney, R.A., Wise, A., Ciruela, F., Chan, W.Y., Emson, P.C., Billinton, A., Marshall, F.H., 2000. The GABAB receptor interacts directly with the related transcription factors CREB2 and ATFx. Proc. Natl. Acad. Sci. U. S. A. 97, 13967–13972.

Williams, N.M., Owen, M.J., 2004. Genetic abnormalities of chromosome 22 and the development of psychosis. Curr. Psychiatry Rep. 6, 176–182.

Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W., David, A.S., Murray, R.M., Bullmore, E.T., 2000. Meta-analysis of regional brain volumes in schizophrenia. Am. J. Psychiatry 157, 16–25.

Wu, X., Gu, J., Grossman, H.B., Amos, C.I., Etzel, C., Huang, M., Zhang, Q., Millikan, R.E., Lerner, S., Dinney, C.P., Spitz, M.R., 2006. Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. Am. J. Hum. Genet. 78, 464–479.

Wyszynski, M., Lin, J., Rao, A., Nigh, E., Beggs, A.H., Craig, A.M., Sheng, M., 1997. Competitive binding of alpha-actinin and calmodulin to the NMDA receptor. Nature 385, 439–442.

Yanagida, O., Kanai, Y., Chairoungdua, A., Kim, D.K., Segawa, H., Nii, T., Cha, S.H., Matsuo, H., Fukushima, J., Fukasawa, Y., Tani, Y., Taketani, Y., Uchino, H., Kim, J.Y., Inatomi, J., Okayasu, I., Miyamoto, K., Takeda, E., Goya, T., Endou, H., 2001. Human L-type amino acid transporter 1 (LAT1): characterization of function and expression in tumor cell lines. Biochim. Biophys. Acta 1514, 291–302.

Yang, C.R., Chen, L., 2005. Targeting prefrontal cortical dopamine D1 and *N*-methyl-D-aspartate receptor interactions in schizophrenia treatment. Neuroscientist 11, 452–470.

Yao, J.K., Reddy, R.D., van Kammen, D.P., 2001. Oxidative damage and schizophrenia: an overview of the evidence and its therapeutic implications. CNS Drugs 15, 287–310.

Yoo, H.W., Warner, C.A., Chen, C.H., Desnick, R.J., 1993. Hydroxymethylbilane synthase: complete genomic sequence and amplifiable polymorphisms in the human gene. Genomics 15, 21–29.

Yurek, D.M., Zhang, L., Fletcher-Turner, A., Seroogy, K.B., 2004. Supranigral injection of neuregulin1-beta induces striatal dopamine overflow. Brain Res. 1028, 116–119.

Yuste, R., Bonhoeffer, T., 2001. Morphological changes in dendritic spines associated with long-term ynaptic plasticity. Annu. Rev. Neurosci. 24, 1071–1089.

Zhou, M., Zhuang, Y.L., Xu, Q., Li, Y.D., Shen, Y., 2004. VSD: a database for schizophrenia candidate genes focusing on variations. Hum. Mutat. 23, 1–7.

Zhu, B.T., 2004. CNS dopamine oxidation and catechol-*O*-methyltransferase: importance in the etiology, pharmacotherapy, and dietary prevention of Parkinson's disease. Int. J. Mol. Med. 13, 343–353.